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Characterisation of human exposure pathways to perfluorinated compounds — Comparing exposure estimates with biomarkers of exposure ☆

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ABSTRACT

Commercially used per- and polyfluorinated compounds (PFCs) have been widely detected in humans, but the sources of human exposure are not fully characterized. The objectives of this study were to assess the relative importance of different exposure pathways of PFCs in a group of Norwegians and compare estimated intakes with internal doses obtained through biomonitoring. Individual PFC intakes from multiple exposure sources for a study group of 41 Norwegian women were estimated using measured PFC concentrations in indoor air and house dust as well as information from food frequency questionnaires and PFC concentrations in Norwegian food. Food was generally the major exposure source, representing 67–84% of the median total intake for PFOA and 88–99% for PFOS using different dust ingestion rates and biotransformation factors of 'precursor' compounds. However, on an individual basis, the indoor environment accounted for up to around 50% of the total intake for several women. Significant positive associations between concentrations of PFCs in house dust and the corresponding serum concentrations underline the importance of indoor environment as an exposure pathway for PFCs. For breast-fed infants, breast milk was calculated to be the single most important source to PFCs by far. The estimated intakes were confirmed by comparing serum concentrations of PFOA and PFOS calculated using PK models, with the corresponding concentrations measured in serum. Even though food in general is the major source of exposure for PFCs, the indoor environment may be an important contributor to human exposure. This study provides valuable knowledge for risk assessment of PFCs and control strategies.

1. Introduction

Per- and polyfluorinated compounds (PFCs) have been used during the last 50 years in many commercial applications including surfactants, lubricants, paints, polishes, paper and textile coatings, food packaging and fire-retarding foams (Kissa, 2001). PFCs comprise a diverse class of chemicals consisting of an alkyl chain which is partly (poly) or fully (per) fluorinated and have different functional groups attached. Among the perfluorinated compounds are the perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkyl sulfonic acids (PFSAs), perfluoroalkyl sulfonamides (FOSAs) and perfluoroalkyl sulfonamidoethanols (FOSEs), while the polyfluorinated compounds comprise e.g. fluorotelomer alcohols (FTOHs).

Concerns about the persistence and bioaccumulative properties of PFCs were raised when the widely used surfactant perfluorooctyl sulfonic acid (PFOS) was found to be ubiquitously distributed in wildlife and human populations worldwide (Houde et al., 2006; Lau et al., 2007). Long elimination half-lives have been observed for perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS) and PFOS in humans (Bartell et al., 2009; Hölzer et al., 2009; Olsen et al., 2007; Seals et al., 2010) and two recent studies indicated long elimination half-lives for perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnDA) as well (Freberg et al., 2010; Nilsson et al., 2010). Animal studies have demonstrated hepatotoxicity, developmental toxicity, immunotoxicity and hormonal effects (Lau et al., 2007). Thus, PFOS fulfills the

Abbreviations: AMAP, Arctic Monitoring and Assessment Programme; EFSA, European Food Safety Authority; FFQ, food frequency questionnaire; FOSA, perfluoroalkyl sulfonamide; FOSE, perfluoroalkyl sulfonamidoethanol; FTOH, fluorotelomer alcohol; LOQ, limit of quantification; MLR, multiple linear regression; POP, persistent organic pollutant; PFCA, perfluoroalkyl carboxylic acid; PFCs, per- and polyfluorinated compounds; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFHpS, perfluoroheptane sulfonic acid; PFOS, perfluorooctane sulfonic acid; PFSA, perfluoroalkyl sulfonic acid; PK model, pharmacokinetic model; TDI, tolerable daily intake.

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criteria of the Stockholm Convention on persistent organic pollutants (POPs) and has been included in the list of restricted chemicals in 2009 (Stockholm Convention on Persistent Organic Pollutants, 2009).

The large historical production volumes and widespread applications of PFCs also in consumer products represent a potential for contamination of the indoor as well as the outdoor environment and thereby also food and drinking water. Dietary exposure has been suggested to be the main exposure route of PFCs in adult general populations (Fromme et al., 2009; Trudel et al., 2008; Vestergren and Cousins, 2009), and we have previously reported significant associations between estimated dietary intakes of PFOA, PFOS and PFUnDA and the corresponding serum concentrations (Haug et al., 2010). In certain cases also contaminated drinking water has been shown to be a major source of exposure (Egeghy and Lorber, 2010; Emmett et al., 2006; Vestergren and Cousins, 2009). Further, the contribution from dust ingestion was estimated to be nearly as great as from food ingestion for 2 years old children in USA (Egeghy and Lorber, 2010). A recent review by Harrad et al. (2010) emphasized the importance of evaluating exposure from ingestion of house dust and inhalation of indoor air. Further, it has been demonstrated that FTOHs can be biodegraded to PFCAs (Nabb et al., 2007) and FOSA/FOSEs can biodegrade to PFSAs (Tomy et al., 2004). Thus, exposure to PFCAs and PFSAs can also occur through degradation of 'precursors' such as FTOHs and FOSA/FOSEs. The knowledge on the relative impact of precursors to the total exposure of PFCs in humans is limited. Vestergren et al. (2008) estimated the relative contribution of precursor compounds to be 2–8% of the total exposure for PFOA and PFOS in an intermediate scenario, but as high as 28–80% in a high-exposure scenario. To our knowledge, no studies have so far considered multiple exposure sources including dust, air and diet enabling comparison of different exposure pathways on an individual basis.

For the youngest children, consumption of breast milk might be an additional source of PFC exposure. Even though the concentrations of PFCs in breast milk are considered to be low compared to blood (Kärrman et al., 2007), Thomsen et al. (2010) showed that the intake of PFCs through breast milk is similar to the dietary intake for Norwegian adults.

The aims of this study were to estimate and compare individual intakes of PFCs from food, drinking water, dust ingestion and inhalation of precursors in indoor air in a group of Norwegian women, and explore relationships between the estimated intakes and the measured serum concentrations. Further, we wanted to calculate the PFC exposure of infants through consumption of breast milk as well as inhalation of indoor air and ingestion of house dust.

2. Materials and methods

2.1. Study subjects

A study group of 41 female volunteers from the Oslo area, Norway was established. (Characteristics are given in Supplemental Material Table S1). Informed consent was obtained from all the participants and the project was approved by the Regional Committee for Medical Research Ethics (S-0711a, 2.2007.260). Samples of house dust as well as indoor air from the women's residences were collected between February and May 2008. Details on the sampling procedures as well as the measured concentrations of PFCs are described in Haug et al. (submitted for publication). The women also donated a serum sample and completed a questionnaire covering demographic information, different life style factors as well as dietary habits. In addition, about half of the women provided a sample of breast milk ($n=19$).

2.2. Data collection

Blood serum (3.5–13 mL) was collected either by general practitioners or a medical laboratory technician at the Norwegian Institute of Public Health, between August 2007 and May 2008. Breast milk ($n=19$) was collected by the women themselves between August 2007 and September 2008. The mothers were provided pre-cleaned screw cap bottles (PE) and the breast milk was obtained by manual expression to avoid potential contamination by breast pumps. The mothers were free to collect the breast milk whenever they liked during the day and sampling could occur on consecutive days as long as the breast milk was frozen between each sampling. Between 30 and 100 mL breast milk was obtained from the women. The samples were stored at below −18 °C until analyses.

Based on the knowledge of decreasing PFC concentrations in breast milk during the lactation period, serum and breast milk samples should ideally have been collected within a short period of time for each woman. Due to practical reasons this was not possible for many of the mothers. As an experiment we back-calculated either the serum or the breast milk concentration as if the samples were collected within a two week period using the models for depuration obtained by Thomsen et al. (2010). Further, the adjusted concentrations were used in the calculations, but only minor changes were observed, both in the linear curves and in the correlation coefficients compared to the curves obtained using the measured concentrations. Thus, the measured concentrations have been used throughout the paper.

2.3. Chemicals analysis of serum and breast milk

The nineteen PFCs, twelve isotope labeled internal standards and all other chemicals used are described elsewhere (Haug et al., 2009b). The serum samples were analyzed according to a previously described method (Haug et al., 2009b), while the breast milk samples were prepared and analyzed using the method by Thomsen et al. (2010). The procedural blanks (serum; $n=6$ and breast milk; $n=3$) analyzed together with the samples, did not contain any of the PFCs above limit of quantification (LOQ). For quantification of PFOS, the total area of the linear and branched isomers was integrated. The relative amount of the branched PFOS isomers was also calculated.

High quality of the serum determinations was assured by analyzing three replicates of three different in-house quality control samples ($n=3\times3$) as well as human serum samples from an interlaboratory comparison study organized by Institute national de santé publique du Québec (Canada) for the Arctic Monitoring and Assessment Programme (AMAP) ($n=3$) (AMAP, 2008). All results from the AMAP interlaboratory comparison were within ±1 SD of the consensus concentrations. The variations in the three replicates of each in-house quality control sample were less than 12% (RSD).

For the breast milk samples high quality of the determinations was assured by analyzing an in-house quality control sample ($n=6$). The relative standard deviations of the six replicates were 6.1% for PFOA and 3.1% for PFOS, the only two PFCs detected in this sample. In addition, the laboratory participated in a proficiency test on determination of PFCs in breast milk and obtained concentrations within ±1 SD of the consensus value for all PFCs found above the LOQ (B. van Bavel, personal communication).

2.4. Calculation of PFC intakes

Due to limited data on concentrations of PFCs in Norwegian food, estimation of dietary intakes were possible only for PFOA, PFUnDA and PFOS, and as PFUnDA was not observed above LOQ in any of the dust samples, intake estimates are presented for PFOS and PFOA only. Information regarding calculation of the intakes is given in the Supplemental Material (text and Table S2). For the 41 women, individual intakes were estimated based on consumption of food

(data from questionnaires) and drinking water (1.41 L/day; Egeghy and Lorber, 2010) as well as from inhalation of indoor air (13.3 m^3/day; Egeghy and Lorber, 2010) and ingestion of dust. For inhalation and dust ingestion three different scenarios based on literature data were established; For dust, scenario 1: 50, scenario 2: 100 or scenario 3: 200 mg/day (U. S. Environmental Protection Agency, 1997). Only direct exposure to PFOS and PFOA (no biotransformation of precursors) was considered, except for air where biotransformation of FOSA/FOSEs to PFOS (scenario 1: 1%, scenario 2: 20% or scenario 3: 100%) and FTOHs to PFOA (scenario 1: 0.02%, scenario 2: 0.5% or scenario 3: 1.7%) was included according to Vestergren et al., 2008. An assumption of 100% absorption was made for all intake estimates. The dietary information used, was obtained from a self-administered food frequency questionnaire (FFQ) focusing on consumption over the last 12 months, with special emphasis on fish and shell fish. Due to limited knowledge and high uncertainty regarding dust ingestion rates and biotransformation factors, three different exposure scenarios were explored both for dust ingestion and inhalation of air while intakes from food and drinking water were regarded as sufficiently certain. This resulted in the calculation of three total intakes.

Norwegian mothers are among the most enthusiastic breast-feeders in the world. Governmental authorities recommend exclusive breast-feeding the first half year (Norwegian Directorate of Health, 2008), and more than 80% of all babies are breast-fed at the age of six months (Andreassen et al., 2001). Further, at this age infants may also ingest considerable amounts of dust by crawling on the floor and by putting toys etc. in their mouth. Thus, for exposure of infants we chose to assess children six months of age, and included consumption of breast milk (700 mL/day), ingestion of dust and inhalation of air (6.8 m^3/day) (Egeghy and Lorber, 2010). The dust ingestion rates and biotransformation factors used were the same as those used for the women. A body weight (bw) of 7 kg was assumed.

2.5. Pharmacokinetic modeling

A first-order pharmacokinetic (PK) model as described by Egeghy and Lorber (2010) was used. The model predicts the blood serum concentration as a function of dose, elimination rate and volume of distribution (i.e. the total amount of a PFC in the body divided by its concentration in the serum). This model is based on an assumption of steady state conditions. The doses used were the total intakes of PFOS or PFOA (women; scenario 1, 2 and 3) in ng/kg bw/day. Elimination half-lives of 4.8 years (Olsen et al., 2007) and 2.3 years (Bartell et al., 2009) were applied for PFOS and PFOA, respectively, while the volumes of distribution were set to 220 mL/kg for PFOS and 140 mL/kg for PFOA, according to Andersen et al. (2006). The applied volume of distribution for PFOA is similar to what Thompson et al. (2010) have arrived at during calibration of a corresponding model using human data.

2.6. Statistics

SPSS version 17.0 (SPSS Inc. Chicago, IL, USA) was used for statistical analyses. The concentrations of all PFCs in serum, breast milk, dust and air below the LOQ was set to LOQ divided by the square root of two. Only values above LOQ were included when exploring the linear relationships between concentrations of PFCs in paired samples of breast milk and serum. A significance level of $p = 0.05$ was used.

Determinants of PFC concentrations in serum were explored for all PFCs being present in more than 40% of all the sample matrices (serum, dust and air). The serum, dust and air concentrations were not normally distributed, hence Spearman rank correlation was used to investigate bivariate correlations. Logarithmic transformation was applied to these variables prior to the multiple linear regression (MLR) analyses. We did a two stage evaluation of the determinants. First we explored bivariate correlations between PFC concentrations in serum and all relevant variables (see Supplemental Material Table S3, S4 and S5). Then all variables with $p<0.2$, were included stepwise into the MLR models. The influence of age and weight of the women were included in the models as these variables have previously been found to be predictors of PFC concentrations in serum (Halldorsson et al., 2008; Haug et al., 2010). In addition, variables found to significantly influence one PFC were included in the models for the other PFCs as well, even though $p>0.2$ in the bivariate correlations. One woman had a PFOA concentration of more than 10 times the median. This observation was identified as an outlier using Dixons Q test and was left out of the bivariate correlations and the MLR analyses. The factors included in the final models were age, weight, number of months since breast-feeding ended, consumption of fish liver, consumption of shellfish and concentrations of the respective PFC in dust.

Associations between concentrations of PFCs in serum and the individual intake estimates of the corresponding PFCs were explored using MLR analyses. Four models were established both for PFOS and PFOA. In models 1 to 3, serum concentrations were compared to the individual total intakes based on the corresponding scenarios 1 to 3. For model 4, serum concentrations were compared to the intakes through the different exposure pathways separately using scenario 1. Information on the number of months since last breast-feeding and on age was included in the MLR models.

3. Results and discussion

3.1. PFC concentrations in serum and breast milk

Up to 11 and 2 PFCs were found in the samples of serum ($n = 41$) and breast milk ($n = 19$), respectively (see Supplemental Material Table S6), in concentrations similar to what has been reported previously in Norway and elsewhere. (Fromme et al., 2009; Haug et al., 2009a; Lau et al., 2007; Thomsen et al., 2010).

Partitioning of PFCs between breast milk and serum was explored, and significant positive correlations for both PFOA ($R = 0.97$, $n = 10$) and PFOS ($R = 0.71$, $n = 19$) were found (Supplemental Material; Figure S1). Average breast milk concentrations were 1.4% and 3.8% of the corresponding serum concentrations for PFOS and PFOA, respectively, i.e. transfer of PFOA to breast milk was more than two times higher than of PFOS. This is in agreement with Thomsen et al. (2010) who reported that the reduction of PFOA concentration in breast milk during the lactation period was about twice that of PFOS (94% vs 37% in one year). A strong correlation between breast milk and serum concentrations of PFOS ($R^2 = 0.69$) was also seen in a Swedish study on 12 women, where the breast milk concentration was about 1% of the serum concentration (Kärrman et al., 2007).

The mean relative proportions of branched PFOS isomers were 22% (14–50%) and 17% (9–29%) in serum and breast milk, respectively. This is similar to what was found in a previous study on breast milk (Thomsen et al., 2010), but lower than what has been reported in a time trend study from Norway on serum samples (Haug et al., 2009a). The discrepancy between the two data sets on Norwegian human serum remains to be clarified. The relative amounts of branched PFOS isomers in serum and breast milk were independent of the concentrations, and significant correlations of branched PFOS isomers between serum and breast milk were seen (Pearson, $R = 0.50$; $p = 0.031$).

3.2. Determinants of serum PFC concentrations

Significant positive associations between the concentrations of PFOA and PFH×S in house dust and the corresponding PFC concentrations in serum were found in MLR models (Supplemental Material; Table S7 and S8). A similar trend was seen for PFOS, however statistically significance was not reached ($p = 0.064$). Further, breast-feeding history was a significant determinant for all PFCs except PFUnDA, both in unadjusted and adjusted models. The nulliparous women were assigned a value of 200 months since last breast-feeding, to avoid missing observations. Increasing PFC concentrations were associated with increasing number of months since breast-feeding the last child. This is in accordance with findings in two other Norwegian studies (Haug et al., 2010; Thomsen et al., 2010). For most PFCs a significant or borderline significant association between consumption of fish liver or shellfish and the serum concentrations were observed, which is in agreement with our previous findings (Haug et al., 2010). Associations between the women's weight and concentrations in serum were observed for all PFCs, except PFNA. The women's age was significantly associated only with the concentration of PFOA in serum. However, similar associations were also observed for PFNA and PFDA, even though they did not reach statistically significance. We have previously shown a strong age dependency for all PFCs (Haug et al., 2010). We believe the contradicting results seen in this study are due to the narrow age span of the women.

3.3. Estimated intakes of PFCs

Route-specific individual intakes for the women were estimated for PFOS and PFOA to examine the relative importance of different exposure pathways (Table 1). Because of limited knowledge on amount of dust ingested and biotransformation rates for 'precursors' to PFOS and PFOA, intakes from dust ingestion and inhalation of indoor air were calculated according to three scenarios, with increasing dust ingestion rates and biotransformation factors. Thus three total intakes were calculated. The median total intakes of PFOS were 0.64, 0.67 and 0.77 ng/kg bw/day for scenario 1, 2 and 3, respectively. Correspondingly, the median PFOA intakes were 0.27, 0.30 and 0.36 ng/kg bw/day. This is in the same range as what has been reported for PFOS and PFOA in other studies on populations exposed to background contamination levels (Egeghy and Lorber, 2010; Fromme et al., 2009; Trudel et al., 2008; Vestergren and Cousins, 2009). When estimating the exposure through inhalation, outdoor air has been left out as PFC concentrations in outdoor air are considerably lower than in indoor air (Egeghy and Lorber, 2010) and Norwegians generally spend more time indoors. However, leaving out the time spent outdoors could lead to an over-estimation of the intake through inhalation. Further, we have not included exposure to PFCs through dermal absorption in the total exposure assessment. The dermal uptake seems to be very limited as demonstrated at least for PFOA (Fasano et al., 2005). For exposure from food, drinking water and house dust, biotransformation of precursors could not be considered due to lack of data on precursor compounds. For indoor air only indirect exposure through precursors was assessed and not direct exposure to PFOS and PFOA. Leaving out these potential sources of exposure could have resulted in an under-estimation of the total intakes.

The relative importance of the specific exposure routes are changing as the dust ingestion rate and the biotransformation factor change (Fig. 1 and Supplemental Material Table S9). Based on the median values in scenario 1, food represented 84%, drinking water 11%, dust 5.2% and indoor air 0.13% of the total intakes for PFOA. Correspondingly, for PFOS food represented 99%, drinking water 0.68%, dust 0.41% and indoor air 0.10% of the total intakes. Thus, food is in general the dominating exposure pathway for PFOS and PFOA in adults.

However, when looking into the intakes of PFOS on an individual basis (Fig. 2), the relative contribution of dust ingestion to the total intakes varied between 0.10 and 26%

Table 1
Estimated intakes of PFOS and PFOA (ng/kg bw/day) from multiple exposure pathways for women a percentile.

			Mean	Min	25th p[a]	50th p[a]	75th p[a]	Max
PFOS	Scenario 1	Food	0.70	0.10	0.47	0.61	0.88	1.9
		Drinking water	0.004	0.003	0.004	0.004	0.005	0.006
		Dust	0.009	0.001	0.002	0.003	0.006	0.080
		Air	0.001	0.000	0.000	0.001	0.001	0.004
		Total	0.71	0.10	0.48	0.62	0.89	2.0
	Scenario 2	Food	0.70	0.10	0.47	0.61	0.88	1.9
		Drinking water	0.004	0.003	0.004	0.004	0.005	0.006
		Dust	0.018	0.002	0.004	0.005	0.011	0.16
		Air	0.019	0.004	0.007	0.015	0.021	0.077
		Total	0.74	0.11	0.49	0.63	0.92	2.1
	Scenario 3	Food	0.70	0.10	0.47	0.61	0.88	1.9
		Drinking water	0.004	0.003	0.004	0.004	0.005	0.006
		Dust	0.036	0.003	0.007	0.011	0.022	0.32
		Air	0.095	0.020	0.036	0.077	0.11	0.38
		Total	0.84	0.13	0.52	0.70	1.02	2.6
PFOA	Scenario 1	Food	0.24	0.076	0.16	0.22	0.29	0.55
		Drinking water	0.031	0.021	0.027	0.030	0.034	0.040
		Dust	0.016	0.004	0.008	0.012	0.020	0.050
		Air	0.001	0.000	0.000	0.000	0.001	0.003
		Total	0.29	0.10	0.20	0.26	0.35	0.64
	Scenario 2	Food	0.24	0.076	0.16	0.22	0.29	0.55
		Drinking water	0.031	0.021	0.027	0.030	0.034	0.040
		Dust	0.032	0.007	0.016	0.025	0.040	0.099
		Air	0.013	0.002	0.007	0.010	0.014	0.081
		Total	0.32	0.11	0.21	0.29	0.38	0.77
	Scenario 3	Food	0.24	0.076	0.16	0.22	0.29	0.55
		Drinking water	0.031	0.021	0.027	0.030	0.034	0.040
		Dust	0.063	0.014	0.032	0.049	0.081	0.20
		Air	0.043	0.006	0.025	0.035	0.049	0.28
		Total	0.38	0.12	0.24	0.33	0.45	1.1

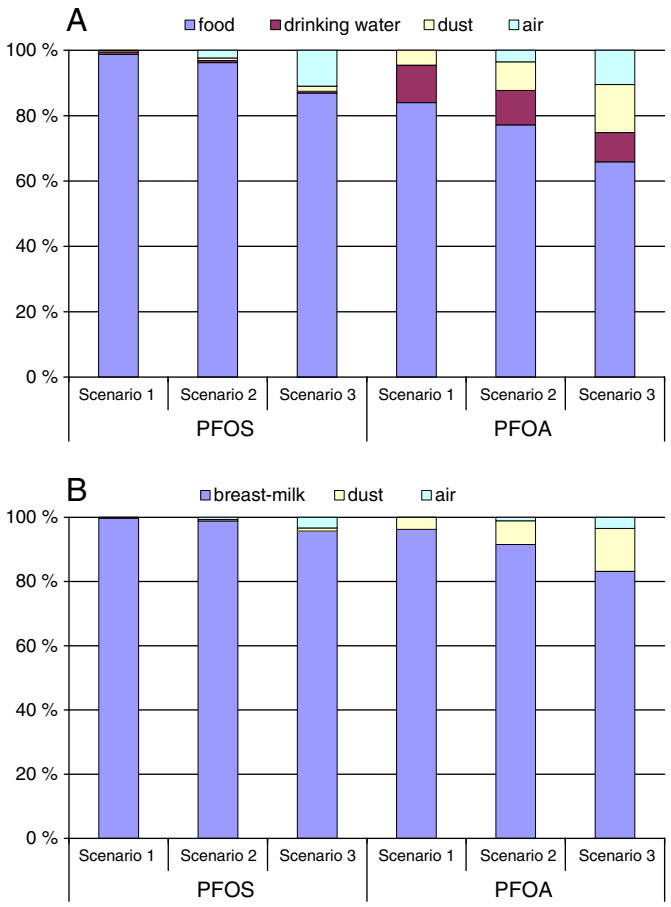

Fig. 1. Relative proportions of intakes from multiple exposure pathways (median values) for the women (A) and at infants six months of age (B).

for scenario 1, while they were in the range of 0.37 to 56% for scenario 3. Based on the biotransformation factor applied in scenario 1 (1%), inhalation of indoor air contributed below 0.77% of the total PFOS. However, when assuming that 100% of the FOSA/FOSE is biotransformed to PFOS (scenario 3) up to 42% of the total intake could come from inhalation of indoor air. Drinking water represented at most 3.3% of the PFOS intake. Thus, the relative importance of the PFOS exposure from dust and indoor air was estimated quite high for some women (up to 61%; scenario 3), but for the majority of women more than 80% of the total exposure originated from food consumption.

For PFOA the influence of the indoor exposure was in general higher than for PFOS. Food contributed to between 56 and 92% of the total PFOA intake for scenario 1, but could be as low as 30% (range 30–84%) based on the assumptions in scenario 3. Drinking water represented 4.6% to 22% of the total PFOA intakes. The relative contribution of indoor air was below 1.2% in scenario 1, while it could be up to 48% in scenario 3. Similarly the relative contribution of dust ingestion varied between 1.7% and 45%. Thus, both for PFOS and PFOA the relative contribution of different exposure pathways varied a lot among the women. This highlights the importance of performing measurements on an individual basis to explore the individual variations.

Benskin et al. (2009) hypothesized that isomer specific biotransformation rates of PFOS-precursors may explain the common observation of enrichment of the branched PFOS isomer profiles in humans, and consequently, that enriched branched PFOS isomer profiles in humans may be a useful tool for tracking sources of PFOS exposure. Thus, we hypothesized that women with the highest relative contribution of the total PFOS intake from inhalation of precursors in indoor air would have a high proportion of branched PFOS isomers in their serum. We explored this using Spearman rank correlation and found indeed significant associations (Scenario 1; $R = 0.33$; $p = 0.038$). This is in agreement with the hypothesis of Benskin et al. (2009) even though we only could consider concentrations of PFOS-precursor in indoor air and not in food.

3.4. Estimated intakes of PFCs for infants

The route-specific intakes estimated for six months old infants are presented in Table 2. The median total intakes ranged from 8.7 to 9.1 ng/kg bw/day for PFOS and 4.3 to 4.9 ng/kg bw/day for PFOA, depending on the dust ingestion rates and biotransformation factors used. The relative importance of the different exposure pathways (medians) are depicted in Fig. 1, demonstrating that consumption of breast milk

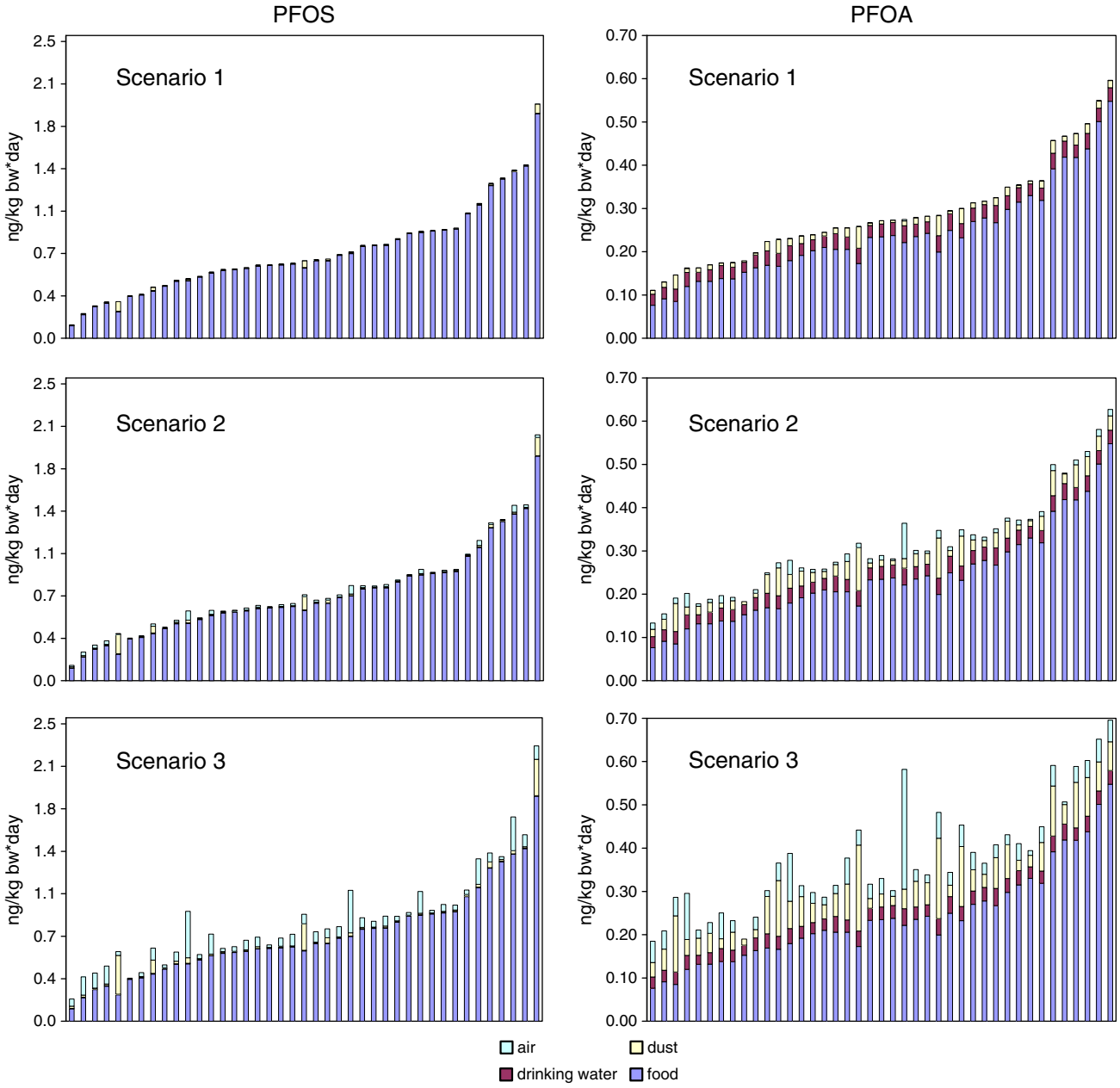

Fig. 2. Clustered bar charts of individual estimated intakes (ng/kg bw/day) for PFOS and PFOA from multiple exposure pathways for the women.

represents more than 94 and 83% of the exposure to PFOS and PFOA, respectively. Thomsen et al. (2010) reported an average reduction of PFOS and PFOA concentrations in breast milk of 3.8 and 7.8% per month during the course of breast-feeding. Thus, the breast milk concentrations were re-calculated to the expected concentration at 6 months of age using these depuration rates, but neither the range nor the median of the relative proportion of different intakes changed much. So far no other studies have compared exposure pathways for infants based on individual measurements of PFC concentrations in breast milk, house dust and indoor air. Egeghy and Lorber (2010) estimated route specific PFOS intakes for 2-year old children, finding that food, ingestion of dust and water represented 42, 36 and 20% of the total intake, respectively. Thus, breast milk is certainly the dominating source of PFCs exposure for exclusively or predominantly breast-fed infants, while the importance of the indoor environment increases after weaning.

The total exposure to PFOS and PFOA for infants (ng/kg bw/day) were 13–16 times higher than the corresponding estimates for adults. The Scientific Panel on Contaminants in the Food Chain within the European Food Safety Authority (EFSA) has established tolerable daily intakes (TDI) for PFOS and PFOA of 150 ng/kg bw/day and 1.5 μg/kg bw/day, respectively (EFSA, 2008). Thus, the maximum estimated intakes of PFOS and PFOA for infants 6 months of age (scenario 3) were only about 5 (PFOS) and 18 (PFOA) times below this TDI. However, it has to be taken into account that TDI are established for lifelong exposure and cannot be applied to the relatively short period of breast-feeding.

3.5. Relationship between estimated dietary intakes and serum concentrations

To explore relationships between estimated intakes of PFOS and PFOA and the corresponding serum concentrations for women, MLR analyses were performed (Table 3). Neither for PFOS nor PFOA significant relationships between the total intakes and the corresponding serum concentrations were seen. However, when the different sources were considered separately, significant positive associations were observed between the concentrations of PFOA in serum and the corresponding intake through dust ingestion (scenario 1). A similar tendency was also observed for PFOS. In contradiction to what was observed in our previous study (Haug et al., 2010), no significant relationships between dietary intake and concentrations of PFOA or PFOS in serum were observed. This could be due to the limited number of participants in the present study, less variation in the consumed food, or insufficient information obtained in the FFQ or concentrations in food. Another plausible explanation could be that the predominance of PFC intakes through food results in a "baseline" serum concentration, while the concentration above this "baseline" might be driven by the wide variation in dust intakes. Hence an association with dust is more likely to be found than with food.

Table 2
Estimated intakes of PFOS and PFOA (ng/kg bw/day) from multiple exposure pathways for infants at around 6 months of age a percentile.

			Mean	Min	25th p[a]	50th p[a]	75th p[a]	Max
PFOS	Scenario 1	Breast-milk	9.3	4.0	5.8	8.7	9.6	25
		Dust	0.11	0.01	0.02	0.02	0.06	0.67
		Air	0.004	0.000	0.001	0.003	0.004	0.014
		Total	9.4	4.0	5.8	8.7	9.7	26
	Scenario 2	Breast-milk	9.3	4.0	5.8	8.7	9.6	25
		Dust	0.23	0.02	0.03	0.04	0.13	1.35
		Air	0.071	0.000	0.026	0.060	0.086	0.28
		Total	9.6	4.0	5.9	8.8	9.8	27
	Scenario 3	Breast-milk	9.3	4.0	5.8	8.7	9.6	25
		Dust	0.46	0.04	0.07	0.09	0.3	2.7
		Air	0.36	0.000	0.13	0.30	0.43	1.4
		Total	10	4.0	6.0	9.1	10	29
PFOA	Scenario 1	Breast-milk	13	2.5	3.5	4.1	9.2	83
		Dust	0.19	0.06	0.12	0.16	0.29	0.40
		Air	0.002	0.000	0.001	0.001	0.003	0.003
		Total	13	2.6	3.6	4.3	9.5	83
	Scenario 2	Breast-milk	13	2.5	3.5	4.1	9.2	83
		Dust	0.39	0.12	0.24	0.33	0.57	0.79
		Air	0.047	0.017	0.038	0.049	0.059	0.069
		Total	13	2.6	3.8	4.5	9.8	84
	Scenario 3	Breast-milk	13	2.5	3.5	4.1	9.2	83
		Dust	0.78	0.23	0.47	0.66	1.1	1.6
		Air	0.16	0.060	0.13	0.17	0.20	0.23
		Total	14	2.8	4.1	4.9	11	85

Anyway, this shows that PFCs in dust might be an important determinant for serum PFC concentrations.

3.6. PK modeling

The estimated intakes were evaluated by comparing serum concentrations of PFOA and PFOS calculated using PK models, with the corresponding concentrations measured in serum. The calculated and measured concentrations were in good agreement (Fig. 3), which indicates that the estimated intakes are reasonable and shows that PK modeling may be a valuable tool in exposure assessment despite the underlying uncertainties. The best agreements between the PK models and the measured serum concentrations were obtained for scenario 1, indicating that the exposure factors in this scenario are most realistic.

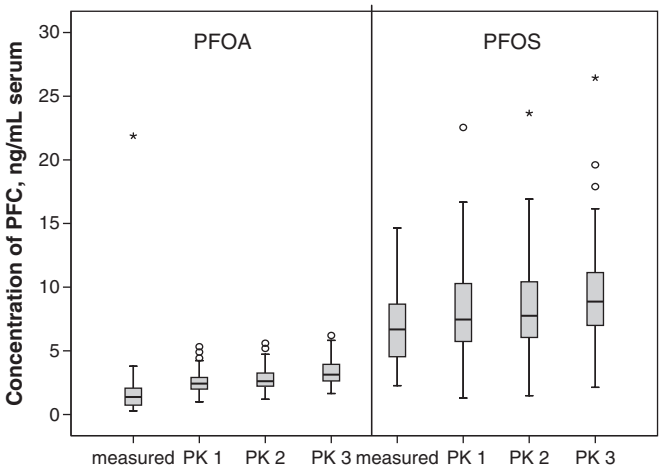

Fig. 3. Box-plot of measured and calculated concentrations using PK modeling and the three scenarios of PFOS and PFOA in serum (ng/mL).

4. Conclusions

To our knowledge this is the first study to assess human exposure pathways based on individual measurements of dust and air and comparisons with biomonitoring. Overall, food was the dominating source of exposure to PFOS and PFOA for this study group. However, the variations in serum concentrations were primarily explained by the intake of PFCs through ingestion of dust in addition to the women's breast-feeding history. This apparent contradiction may be explained by little variation in dietary intakes in our study group, but highly variable PFC concentrations in indoor air and dust. Consequently, the relative importance of exposure to PFOS and PFOA from the indoor environment varied a lot and contributed considerably for several individuals. Dust and indoor air represented more than 40% of the PFOA exposure for one fourth of the women in the scenario comprising high dust ingestion. Although the number of investigated households was limited to 41 for practical reasons and indoor air and house dust were sampled only once, our findings strongly suggest that the indoor environment is an important factor when characterizing human exposure to PFCs. Thus, more efforts are needed to explore the presence and concentrations of PFCs indoors in homes and other microenvironments. Further, better knowledge on the actual amount

Table 3
Unadjusted and adjusted models for relationships between serum concentrations and estimated intakes of selected PFCs.

	Log serum PFOA				Log serum PFOS			
	Model 1	Model 1	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
	β (*p*)	β (*p*)	β (*p*)	β (*p*)	β (*p*)	β (*p*)	β (*p*)	β (*p*)
Number of months since breastfeeding ended	**0.003 (0.000)**	**0.003 (0.000)**	**0.003 (0.000)**	**0.003 (0.000)**	**0.001 (0.002)**	**0.001 (0.002)**	**0.001 (0.002)**	**0.002 (0.001)**
Age, years	**0.017 (0.038)**	**0.017 (0.037)**	**0.018 (0.036)**	**0.020 (0.010)**	0.004 (0.60)	0.004 (0.61)	0.003 (0.65)	0.003 (0.73)
Log total intake (scenario 1), ng/kg bw /day	0.002 (0.99)				0.052 (0.58)			
Log total intake (scenario 2), ng/kg bw/day		0.032 (0.90)				0.058 (0.54)		
Log total intake (scenario 3), ng/kg bw /day			0.073 (0.78)				0.075 (0.41)	
Log intake of food, ng/kg bw /day				–0.16 (0.35)				0.074 (0.57)
Log intake of dust, (scenario 1) ng/kg bw /day				**0.37 (0.005)**				0.096 (0.22)
Log intake of air, (scenario 1) ng/kg bw /day				–0.23 (0.058)				0.009 (0.93)
R^2	0.46	0.46	0.46	0.59	0.25	0.25	0.26	0.30

Figures in **bold** are significant ($p<0.050$).
Areas in gray; variables not relevant for the respective models.

of dust that is ingested and on biotransformation factors of 'precursors' would be highly valuable. For six months old infants in Norway, breast milk was estimated to be the predominant source of PFC exposure, and the maximum estimated intakes were relatively close to the present TDIs for lifelong exposure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.envint.2011.01.011.

References

AMAP. AMAP ring test for persistent organic pollutants in human serum, 2008, round 2. Available:http://www.inspq.qc.ca/ctq/paqe/amap/rapports.asp?Page=2c&partie=2&Lg=en&PCI=62008 [accessed 16 November 2010].

Andersen ME, Clewell III HJ, Tan YM, Butenhoff JL, Olsen GW. Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys — Probing the determinants of long plasma half-lives. Toxicology 2006;227:156–64.

Andreassen M, Bale M, Kaaresen PI, Dahl LB. Breastfeeding in Tromsø before and after «the Baby-Friendly Hospital Initiative». Tidsskrift for den norske legeforening 2001;121:3154–8 [in Norwegian].

Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 2009;118:222–8.

Benskin JP, Holt A, Martin JW. Isomer-specific biotransformation rates of a perfluorooctane sulfonate (PFOS)-precursor by cytochrome P450 isozymes and human liver microsomes. Environ Sci Technol 2009;43:8566–72.

EFSA. Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts. EFSA J 2008;653:1-131.

Egeghy PP, Lorber M. An assessment of the exposure of Americans to perfluorooctane sulfonate: a comparison of estimated intake with values inferred from NHANES data. J Expo Sci Environ Epidemiol 2010:1-19.

Emmett EA, Shofer FS, Zhang H, Freeman D, Desai C, Shaw LM. Community exposure to perfluorooctanoate: relationships between serum concentrations and exposure sources. J Occup Environ Med 2006;48:759–70.

Fasano WJ, Kennedy GL, Szostek B, Farrar DG, Ward RJ, Haroun L. Penetration of ammonium perfluorooctanoate through rat and human skin in vitro. Drug Chem Toxicol 2005;28:79–90.

Freberg BI, Haug LS, Olsen R, Daae HL, Hersson M, Thomsen C, et al. Occupational exposure to airborne perfluorinated compounds during professional ski waxing. Environ Sci Technol 2010;44:7723–8.

Fromme H, Tittlemier SA, Völkel W, Wilhelm M, Twardella D. Perfluorinated compounds — exposure assessment for the general population in western countries. Int J Hyg Environ Health 2009;212:239–70.

Halldorsson TI, Fei CY, Olsen J, Lipworth L, Mclaughlin JK, Olsen SF. Dietary predictors of perfluorinated chemicals: a study from the Danish National Birth Cohort. Environ Sci Technol 2008;42:8971–7.

Harrad S, de Wit CA, Abdallah MA-E, Bergh C, Björklund JA, Covaci A, et al. Indoor contamination with hexabromocyclododecanes, polybrominated diphenyl ethers, and perfluoroalkyl compounds: an important exposure pathway for people? Environ Sci Technol 2010;44:3221–31.

Haug LS, Thomsen C, Becher G. Time trends and the influence of age and gender on serum concentrations of perfluorinated compounds in archived human samples. Environ Sci Technol 2009a;43:2131–6.

Haug LS, Thomsen C, Becher G. A sensitive method for determination of a broad range of perfluorinated compounds in serum suitable for large-scale human biomonitoring. J Chromatogr A 2009b;1216:385–93.

Haug LS, Thomsen C, Brantsæter AL, Kvalem HE, Haugen M, Becher G, et al. Diet and particularly seafood are major sources of perfluorinated compounds in humans. Environ Int 2010;36:772–8.

Hölzer J, Göen T, Rauchfuss K, Kraft M, Angerer J, Kleeschulte P, et al. One-year follow-up of perfluorinated compounds in plasma of German residents from Arnsberg formerly exposed to PFOA-contaminated drinking water. Int J Hyg Environ Health 2009;212:499–504.

Houde M, Martin JW, Letcher RJ, Solomon KR, Muir DCG. Biological monitoring of polyfluoroalkyl substances: a review. Environ Sci Technol 2006;40:3463–73.

Kärrman A, Ericson I, van Bavel B, Darnerud PO, Aune M, Glynn A, et al. Exposure of perfluorinated chemicals through lactation: levels of matched human milk and serum and a temporal trend, 1996–2004, in Sweden. Environ Health Perspect 2007;115:226–30.

Kissa E. Fluorinated surfactants and repellants. 2 ed. New York: Marcel Dekker Inc; 2001.

Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol Sci 2007;99:366–94.

Nabb DL, Szostek B, Himmelstein MW, Mawn MP, Gargas ML, Sweeney LM, et al. In vitro metabolism of 8–2 fluorotelomer alcohol: interspecies comparisons and metabolic pathway refinement. Toxicol Sci 2007;100:333–44.

Nilsson H, Kärrman A, Westberg H, Rotander A, van Bavel B, Lindström G. A time trend study of significantly elevated perfluorocarboxylate levels in humans after using fluorinated ski wax. Environ Sci Technol 2010;44:2150–5.

Norwegian Directorate of Health. The Norwegian Action Plan on Nutrition (2007–2011) Recipe for a healthier diet. Available:http://www.helsedirektoratet.no/ernaering/publikasjoner/handlingsplaner/norwegian_action_plan_on_nutrition_1048842008 [accessed 16 November 2010].

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 2007;115:1298–305.

Seals R, Bartell SM, Steenland K. Accumulation and clearance of PFOA in current and former residents of an exposed community. Environ Health Perspect 2010, doi:10.1289/ehp. 1002346 [online 22 September 2010].

Stockholm Convention on Persistent Organic Pollutants (POPs). Available:http://chm.pops.int/2009 [accessed 16 November 2010].

Thompson J, Lorber M, Toms LL-M, Kato K, Calafat AM, Mueller JF. Use of simple pharmacokinetic modeling to characterize exposure of Australians to perfluorooctanoic acid and perfluorooctane sulfonic acid. Environ Int 2010;36:390–7.

Thomsen C, Haug LS, Stigum H, Frøshaug M, Broadwell SL, Becher G. Changes in concentrations of perfluorinated compounds, polybrominated diphenyl ethers and polychlorinated biphenyls in Norwegian breast-milk during twelve months of lactation. Environ Sci Technol 2010, doi:10.1021/es1021922 [online 23 November 2010].

Tomy GT, Tittlemier SA, Palace VP, Budakowski WR, Braekevelt E, Brinkworth L, et al. Biotransformation of N-ethyl perfluorooctanesulfonamide by rainbow trout (Onchorhynchus mykiss) liver microsomes. Environ Sci Technol 2004;38:758–62.

Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbuhler K. Estimating consumer exposure to PFOS and PFOA. Risk Anal 2008;28:251–69.

U. S. Environmental Protection Agency. Exposure Factors Handbook; EPA/600/P-95/002. Washington, DC: EPA; 1997.

Vestergren R, Cousins IT. Tracking the pathways of human exposure to perfluorocarboxylates. Environ Sci Technol 2009;43:5565–75.

Vestergren R, Cousins IT, Trudel D, Wormuth M, Scheringer M. Estimating the contribution of precursor compounds in consumer exposure to PFOS and PFOA. Chemosphere 2008;73:1617–24.